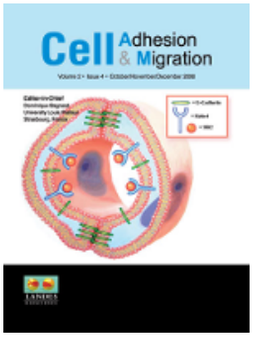

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Special Focus: Recent Advances in the Cellular and Molecular Mechanisms Underlying Synaptic Plasticity

Hormonal regulation of hippocampal dendritic morphology and synaptic plasticity

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Key words: synaptic plasticity, leptin, estrogen, insulin, hippocampus, LTD, LTP

The peripheral functions of hormones such as leptin, insulin and estrogens are well documented. An important and rapidly expanding field is demonstrating that as well as their peripheral actions, these hormones play an important role in modulating synaptic function and structure within the CNS. The hippocampus is a major mediator of spatial learning and memory and is also an area highly susceptible to epileptic seizure. As such, the hippocampus has been extensively studied with particular regard to synaptic plasticity, a process thought to be necessary for learning and memory. Modulators of hippocampal function are therefore of particular interest, not only as potential modulators of learning and memory processes, but also with regard to CNS driven diseases such as epilepsy. Hormones traditionally thought of as only having peripheral roles are now increasingly being shown to have an important role in modulating synaptic plasticity and dendritic morphology. Here we review recent findings demonstrating that a number of hormones are capable of modulating both these phenomena.

Introduction

It is well documented that hormones play a vital role in the regulation and processing of numerous biochemical pathways throughout the body. Until recently, it was thought that hormonal regulation of such processes was restricted largely to the periphery. However, in recent years it has emerged that a range of hormones can be found within the CNS along with complimentary receptors capable of translating hormonal signals into biological actions. These hormone receptor complexes have been shown to have a wide variety of modulatory actions at the neuronal level, no more so than in the hippocampus. Since the early 1950's the hippocampus has been recognised to play a fundamental role in certain forms of learning and memory. It is an area where synaptic plasticity, thought to be the cellular correlate of learning and memory, has been extensively investigated and therefore hormonal modulation of neuronal function in the hippocampus is of great interest and has wide spread implications. Although a number of hormonal systems have been shown to modulate hippocampal function, the largest bodies of work center around estrogens, leptin and insulin. These are exciting and rapidly expanding fields with regard to hippocampal modulation and for this reason we have focused this review on some of the recent work investigating the modulation of hippocampal dendritic morphology and synaptic plasticity mediated by these hormones.

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Leptin

Leptin is a 167 amino acid protein produced almost exclusively in adipose tissue and is found to circulate in the plasma at levels relative to body fat tissue.[1,2] It is well documented that leptin acts on a number of peripheral tissues, but there is strong evidence that leptin can cross the blood brain barrier and act upon targets within the CNS. Moreover, leptin mRNA has been described in a number of brain regions giving rise to the possibility leptin may be synthesised and released from within the CNS itself.[3] Interest in leptin initially focused on its centrally mediated weight-reducing effects and on the potential for using the leptin/leptin receptor axis to develop therapeutic drugs to treat obesity.

The most widely documented functions of leptin within the CNS are found to be in the hypothalamus, where leptin is involved in regulating energy homeostasis,[4] bone formation,[5] reproduction[6] and the hypothalamic-pituitary-adrenal axis.[7] It has emerged recently however that the functions of leptin within the CNS are not restricted solely to the hypothalamus, but that leptin is involved in a diverse array of processes across the CNS, most notably in the hippocampus.[8-10]

The leptin receptor (Ob-R) was first cloned in 1995 from the mouse choroid plexus.[11] Since then, six leptin receptor isoforms, generated by alternate splicing of the *db* gene have been identified in rodents.[12] The six leptin receptor isoforms are termed Ob-Ra to Ob-Rf and have identical extracellular, N-terminal domains. The differences between the isoforms occur at the intracellular C-terminal domains. All isoforms except Ob-Re have a 34 amino acid transmembrane domain. Ob-Re is thought to act as a soluble receptor within the plasma facilitating leptin transport. The membrane spanning isoforms of the leptin receptor are divided into two categories based upon the length of the c-terminal domain. Ob-Ra, c, d and f

have a shorter intracellular domain and are thus termed short forms whilst Ob-Rb has a larger intracellular domain and is thus termed the long form. Although membrane bound short forms of the receptor are able to activate certain signalling cascades, their major role is likely to be related to leptin internalization and degradation.[13] Another possibility is that they are involved in leptin clearance or receptor mediated transport into the brain[14] (reviewed in ref. 15). The longer C terminus of Ob-Rb contains 302 residues in which reside a number of motifs which facilitate the initiation of various downstream signalling cascades.

In line with leptin's reported regulation of hypothalamic function, levels of leptin Ob-Rb mRNA are found to be particularly high in specific regions of the hypothalamus, that are involved in regulating food intake and body weight.[16-19] To date, a number of studies have found high levels of Ob-Rb mRNA expression in several CNS regions including the amygdala, cerebellum, brainstem, substantia nigra and also the hippocampus.[18-21] As well as in the hypothalamus, particularly high levels (relative to overall CNS expression) of Ob-R mRNA and immunoreactivity are apparent in hippocampal CA1 and CA3 regions as well as in the dentate gyrus.[19,20,22] In primary hippocampal cultures, leptin receptors have been shown to be expressed on pyramidal neurons and on glial cells.[23] Moreover, leptin receptor immunostaining is found at axonal and somato-dendritic regions and colocalises with the synaptic marker, synapsin I,[23] suggesting it is localised to synapses. Again, the presence and indeed the high level of expression of both Ob-Rb mRNA and Ob-Rb itself, suggests a role for leptin in the regulation of hippocampal function. It is also evident that Ob-Rb is absent in the choroid plexus, meninges, and also surrounding blood vessels, yet a probe recognizing all known forms of the leptin receptor indicates expression in these areas.[18] This suggests expression of the short isoforms, adding support to the idea that they may be involved in transport of leptin into the brain. As more evidence emerges it is becoming apparent that leptin plays a major role in the regulation of hippocampal synaptic transmission, as well as synaptic plasticity and dendritic morphology. Although some of the studies above have focused on the long form Ob-Rb receptor, it should be remembered that many have looked at general Ob-R mRNA or Ob-R expression. It is likely that effects in these brain regions are mediated by Ob-Rb, however in the absence of isoform specific antagonists we cannot rule out the involvement of other isoforms.

The ability to regulate synaptic strength is a critical feature of the CNS and is thought to underlie processes such as learning and memory. Long-term potentiation (LTP) and long-term depression (LTD) have been studied extensively in the hippocampus to understand the mechanisms of synaptic plasticity.[24,25] Recent evidence has shown that leptin not only regulates hippocampal synaptic transmission per se, but can also regulate different forms of hippocampal synaptic plasticity. Strong evidence that leptin is able to regulate both hippocampal LTP and LTD comes from studies of rodents with Ob-R mutations (either *db/db* mice or *fa/fa* rats) exhibiting both reductions in LTP and LTD[26] as recorded in the CA1 region of acute hippocampal slices. Moreover these rodent strains also show impaired spatial memory in a variety of behavioural tests.[26,27] Conversely, direct administration of leptin into the hippocampus has been shown to improve learning and memory[28,29] as well as to facilitate LTP.[30]

NMDA receptors contribute little to basal synaptic transmission, but are crucial for the induction of certain forms of synaptic plasticity. Leptin has been shown to selectively enhance NMDA receptor-mediated synaptic currents at CA1 synapses in acute hippocampal slices.[31] Furthermore, exposure of acute hippocampal slices to leptin promotes the conversion of short-term potentiation (STP; induced by primed burst stimulation) into LTP.[31] As part of this same study, activation of leptin receptors increased NMDA receptor mediated currents in Xenopus oocytes expressing recombinant NMDA receptor channels. It seems therefore that leptin is able to modulate hippocampal LTP via facilitation of NMDA receptor function. Changes in the morphology and/or the density of dendritic spines have been shown to contribute to enhanced synaptic efficacy following hippocampal LTP.[32] In this respect, it has recently been shown that, in an NMDA receptor dependent manner, leptin rapidly enhances the motility and density of dendritic filipodia in cultured hippocampal neurones and enhances the number of synapsin I positive puncta seen within these cells.[33]

The signalling cascades activated downstream of leptin receptors are much the same as other members of the class I cytokine receptor superfamily and utilise associated janus tyrosine kinases (JAKs). Ligand binding to the leptin receptor results in transphosphorylation of JAK2 and phosphorylation of receptor tyrosine residues, Tyr^{1138} and Tyr^{985}, on the intracellular domain. This leads to the activation of various downstream signalling molecules, including the STAT (signal transducers and activators of transcription) family of transcription factors, insulin receptor substrate (IRS) proteins, phosphoinositide 3-kinase (PI3-kinase) and adaptor proteins associated with Ras-Raf-MAPK (mitogen-activated protein kinase) signalling cascade.

Several studies have examined the cell signalling cascades coupling leptin receptor activation to the modulatory effects on hippocampal synaptic plasticity. The facilitation of NMDA receptor mediated currents was found to be dependent on both PI3 kinase and the MAPK, ERK.[31] Conversely, the rapid increase in motility and density of dendritic filipodia and subsequent enhancement of the density of synaptic labelling was shown to be independent of PI3 kinase, but was dependent on MAPK.[33] Several lines of evidence suggest different localization of different NR2, NMDA receptor subunits within the hippocampus; NR2A containing NMDA receptors being predominantly synaptic whilst NR2B are predominantly extrasynaptic.[34,35] The rapid increase in motility and density of dendritic filipodia induced by leptin is dependent upon synaptic, i.e., NR2A containing, NMDA receptors as opposed to NR2B. Interestingly, a number of studies suggest that activation of NR2A containing NMDA receptors is a pre-requisite for the induction of hippocampal an cortical LTP, whereas NR2B containing NMDA receptors are activated during LTD.[36,37]

As well as modulating hippocampal LTP, leptin has been recently shown to induce a novel form of hippocampal LTD, induced under conditions of increased excitability.[38] Leptin induced LTD shares many characteristics with synaptically induced NMDA receptor-dependent LTD, i.e., NMDA receptor dependence, postsynaptic expression and mGluR-independence. The signalling mechanisms underlying this form of LTD do differ from that of low frequency stimulation (LFS)-induced LTD though; leptin-induced LTD is negatively regulated by PI3-kinase and serine/threonine phosphatases 1/2A.[38]

Insulin

Insulin is a 6 KDa, protein which is synthesized in significant quantities by pancreatic β-cells. Appropriate stimulation of β-cells causes secretion of insulin by exocytosis which then diffuses into islet capillary blood. Binding of insulin to the insulin receptor then regulates the uptake of glucose from the circulation. It is well established that insulin regulates blood glucose levels in this way and, much like leptin, for many years its actions were believed to be restricted to the periphery since insulin was believed to be incapable of crossing the blood brain barrier. It was later discovered that insulin receptors were present in the CNS, originally identified through in vitro binding studies.[39-41] Further studies identified insulin receptors in both neurons and glia throughout the rat brain[42] and more specifically, the β subunit colocalised with synaptophysin in cultured hippocampal neurons as well as being enriched in synaptosome and PSD fractions.[43] Moreover, insulin was later shown to in fact be capable of crossing the blood brain barrier[44] and there is evidence to suggest it may even be synthesized and released by neurons.[45-47] This mounting evidence all implicates a functional role for insulin within the CNS. Indeed, it is now established that insulin influences several CNS functions, including hypothalamic driven feeding,[48] excitatory and inhibitory synaptic transmission[49-51] and neuronal survival.[52] Moreover, dysfunctional insulin signalling is thought to contribute to the development of neurodegenerative disorders such as Alzheimer's disease.[53]

Insulin binding to the insulin receptor leads to intracellular recruitment of insulin receptor substrates and activation of PI3K signalling.[54-56] In addition, recruitment of the adaptor protein SHC to the insulin receptor leads to activation of the ERK 1/2 pathway.[54,57] It is thought that insulin activation of ERK 1/2 may underlie changes in synaptic plasticity and hippocampal dependent learning and memory.[58-60] A role for PI3K is also emerging, as PI3K signalling has been implicated in the induction and maintenance of LTP[61,62] and specific forms of LTD.[63]

There is a growing body of evidence to suggest that insulin, like leptin, can influence synaptic plasticity in the CNS, and more specifically in the hippocampus. Brief application of insulin to hippocampal slices evokes LTD of excitatory synaptic transmission.[64-66] Similar to both synaptically induced LTD (evoked by LFS) and leptin-induced LTD, LTD induced by insulin is dependent upon NMDA receptor activation, is expressed postsynaptically and is mGluR-independent. A number of downstream signalling pathways have been implicated in insulin-induced LTD, including PI3K and PKC.[65,66] Recent studies suggest that the mechanism involves tyrosine phosphorylation of the GluR2 AMPA receptor subunit[67] and internalization of GluR2 containing AMPA receptors.[64,65]

Contrastingly, cell surface expression of the GluR1 AMPA receptor subunit increases following exposure of hippocampal neurons to insulin.[64,68] Interestingly, increases in cell surface GluR1 expression are also thought to underlie hippocampal LTP.[69] Therefore, like leptin, insulin has the unusual capacity to increase as well as decrease synaptic efficacy. Insulin also enhances NMDA receptor mediated currents in hippocampal neurons[70] and promotes an increase in the cell surface density of NMDA receptors.[51] This potentiation of NMDA currents is dependent upon both tyrosine phosphorylation and PKC.[70,71] As these effects are likely to lower the threshold for the induction of plasticity it is not surprising that insulin shifts the frequency response curve of synaptic plasticity to the left.[66] Stimulation of rat hippocampal slices with insulin also rapidly increases the protein expression of PSD-95 in the CA1 area in a PI3K dependent manner.[72] As PSD-95 functions as a scaffold protein, assembling a specific set of signalling proteins around the NMDA receptor,[73] regulation of PSD-95 might provide an additional molecular mechanism by which insulin could modulate hippocampal synaptic plasticity.

To date, there is little evidence to suggest that insulin, via activation of insulin receptors, modulates hippocampal dendritic morphology. However insulin like growth factor 1 (IGF-1) does promote increased dendritic branching in cortical, pyramidal neurons[74] and furthermore cortical neurons from IGF1$^{-/-}$ mice exhibit a reduction in dendritic spine density.[75] Given that insulin has a high affinity for and can signal via IGF-1 receptors, it raises the possibility that insulin can also modulate dendritic morphology. Furthermore, there is evidence to suggest that insulin modulates dendritic growth and neurite outgrowth in a number of brain regions and cell types (reviewed in refs. 52 and 76). Modulation of hippocampal dendritic morphology by insulin is clearly an important area of research which needs to be pursued.

Estrogens

Early studies of estrogens focussed on reproduction and estrogenic actions upon reproductive target organs. As with so many hormones, it has become evident that estrogens acts to influence many other behaviors including modulating forms of learning and memory as well as other cognitive functions (reviewed in ref. 77).

Estrogenic effects within the CNS and more specifically the hippocampus are mediated by estrogens receptors (ERs). There is a wide body of evidence to support estrogen signalling mediated by both nuclear and membrane/synaptically located ERs.[78,79] Genomic signalling (via nuclear receptors) involves nuclear estrogen-receptor complexes binding estrogen response elements (EREs) in the DNA and regulating gene transcription. Non-genomic signalling (via membrane bound receptors) involves membrane bound receptors activating intracellular cascades upon estrogens binding. To date, evidence suggests that both these methods of signalling occur in a number of hippocampal cell types shown to mediate estrogenic effects.

Estrogen receptor α (ERα) and estrogen receptor β (ERβ) are the best characterized estrogen receptors and both are expressed throughout the hippocampal formation.[80-82] Both receptor subtypes have the potential to mediate nuclear as well as membrane associated effects.[83] Other receptor systems associated with estrogens exist in the CNS, but to date remain poorly understood.[84]

The primary source of CNS estrogens are derived from the periphery. In females, estrogen synthesis occurs in the ovaries where testosterone is converted into estradiol within the granulosa cells. This same process occurs in the gonads of males, but to a much lesser extent. Evidence suggests that, like insulin and leptin, estrogens can be transported across the blood brain barrier allowing it to mediate processes within the CNS. Local synthesis of estrogens within the CNS is also a possibility, specifically within the hippocampus. It has been demonstrated in vitro that hippocampal neurons can synthesise estradiol,[85-88] raising the possibility that locally produced estradiol may mediate estrogenic sensitive hippocampal effects.

However, evidence for local production of estrogens to date stem, only from studies of cultured cells or isolated tissue and as of yet no clear evidence exists that estrogens are synthesised in vivo in the hippocampus.

The distribution of ERs within the hippocampus is contentious. ERα and ERβ have been reported throughout all principle cells of the hippocampus as well as in glial cells and different types of GABAergic interneuron (reviewed in ref. 89). Early studies suggested that ERs were principally expressed in GABAergic cells and that estrogens regulate hippocampal activity via modulation of inhibition. Electron microscopy studies have also identified ERα and ERβ in numerous sub-cellular locations,[90,91] but limitations of current antibodies and the fact that ERs have been shown to be differentially regulated at different stages of the oestrous cycle may go some way to explaining the above discrepancies. What is without doubt is that ERs are expressed throughout the hippocampus, although as to what extent remains contentious and that they mediate the ability of estrogens to modulate hippocampal dendritic morphology and synaptic plasticity.

Despite conflicting data as to the exact location and expression levels of ERs in the hippocampus, it is clear that estrogens have a profound effect upon dendritic morphology, particularly at the synaptic level. Ovariectomy in rats decreases the density of dendritic spines in the CA1 region of the hippocampus; an effect that can be reversed by estradiol replacement.[92,93] Furthermore, estradiol increases spine density in rat primary hippocampal neurons in culture.[94] A similar change in spine and synapse density also occurs within the natural oestrous cycle. Rats in late proestrus have a 30% higher density of spines in the CA1 than in late oestrus.[95] Proestrus rats also have a higher proportion of "mushroom" as opposed to "stubby" spines, with evidence suggesting "mushroom" shaped spines to be a more mature and stronger subset of spines.[95,96] Thus as well as increasing spine size, estradiol may play a role in the maturation of dendritic spines.

Consistent with estradiol increasing spine density, estradiol also increases excitatory synaptic contact when observed at the ultrastructural level.[97] Increases in spine density correlate with an increase in the number of pre-synaptic boutons; estadiol increases the number of synapses by 25%.[93] This data, obtained through electron microscopy, provides direct evidence of an increase in the number of synapses in response to estradiol. More recent evidence also shows increases in the molecular components of both postsynaptic spines and presynaptic boutons in response to estradiol. In the CA1 region, levels of synaptophysin, syntaxin, spinophilin and PSD-95 all increase in response to estradiol exposure in both ovariectomised rats[98,99] and in cultured hippocampal neurons.[94,98,100,101]

As far back as 1980 it was reported that estradiol could acutely modulate hippocampal excitability. Electrophysiological studies have shown acute modulation of synaptic events, presumably via membranous ERs. Application of estradiol to hippocampal slices increased the amplitude of synaptically evoked population spikes in the CA1 region of the hippocampus.[102] Subsequently 17β estradiol was reported to increase the CA1, dendritic fEPSP,[103-105] a finding more recently extended to both the dentate gyrus and CA3 regions of the hippocampus.[106] The studies outlined above highlight gross effects on a population of neurons, but single cell recordings largely mirror these results.[107,108] Enhancement of AMPA receptor mediated synaptic transmission by estradiol is independent of NMDA receptor activation, however, NMDA receptor mediated EPSPs can also be facilitated.[103]

Given the marked effects of estradiol on basal synaptic transmission and dendritic morphology in the hippocampus it is not surprising that estradiol also acts as a modulator of hippocampal synaptic plasticity. Indeed, the magnitude of LTP elicited by brief trains of high frequency stimulation (HFS) is greater in female rats during proestrus.[109] Furthermore, ovariectomised rats treated with estradiol were found to show facilitation of hippocampal LTP,[110] an enhancement of hippocampal LTD[111] as well as a reduction in the frequency threshold for the induction of hippocampal LTD.[112] These effects of estradiol may also be dependent upon age as in slices from 3–4 week old rats, estradiol has been reported to suppresses hippocampal LTP.[113]

As previously discussed, the ability of synapses to undergo long-lasting alterations in efficacy, via the process of synaptic plasticity, is thought to be necessary for learning and memory.[24] The hippocampus is a major mediator of spatial learning and memory and it has recently been demonstrated that learning induces LTP in the hippocampus in vivo.[114] In keeping with this, as well as facilitating LTP and LTD, estradiol enhances the performance of rodents in spatial learning tasks.[115-118] Furthermore, in a manner similar to studies on receptor distribution, spine modulation and synaptic physiology, the performance of rodents in memory tasks fluctuates across the oestrus cycle and shifts in the preferred learning strategy have been observed.[115]

It is unclear whether the actions of estrogens discussed above are mediated via nuclear or membranous ERs. Nuclear estradiol binding and ERα immunoreactivity has been seen in hippocampal GABAergic interneurones[119] with nuclear ERβ seen in astrocytes[120] in the hippocampus. This raises the possibility that some estrogenic effects in the hippocampus, especially those involving mediation of GABAergic cells may occur via a genomic effect. Nuclear estradiol binding has also been seen in the basal forebrain which projects to the hippocampal formation.[121] However, it should be noted that there is no direct evidence providing a function for these nuclear hippocampal receptors in the forebrain.

As alluded to earlier, non genomic signalling through ERs has been identified outside the nucleus. The extranuclear receptors which mediate this signalling act by coupling to G proteins, growth factor receptors, and intracellular kinases signalling both rapid hormonal actions and also more delayed effects on gene transcription by activating intracellular signal cascades.[79,122] These receptors are well positioned to process many of the effects described above e.g., on axonal terminals and also on dendritic spines.[90,123] Many of the estrogenic effects described above occur too quickly to be attributable to gene transcription and so it is more likely that they are mediated via non nuclear receptors. Furthermore some of the effects described are post-transcriptional, suggesting effects on protein translation.[98,101]

It is clear that the available evidence is inconclusive as to which receptor systems mediate many of the modulatory effects of estrogens on hippocampal dendritic morphology and synaptic plasticity. However, a recent study has shown that selective agonists for ERβ increase key synaptic proteins, an effect absent in ERβ knockout mice.[124] Furthermore, this same study demonstrated increased dendritic branching, increased spine density and improved

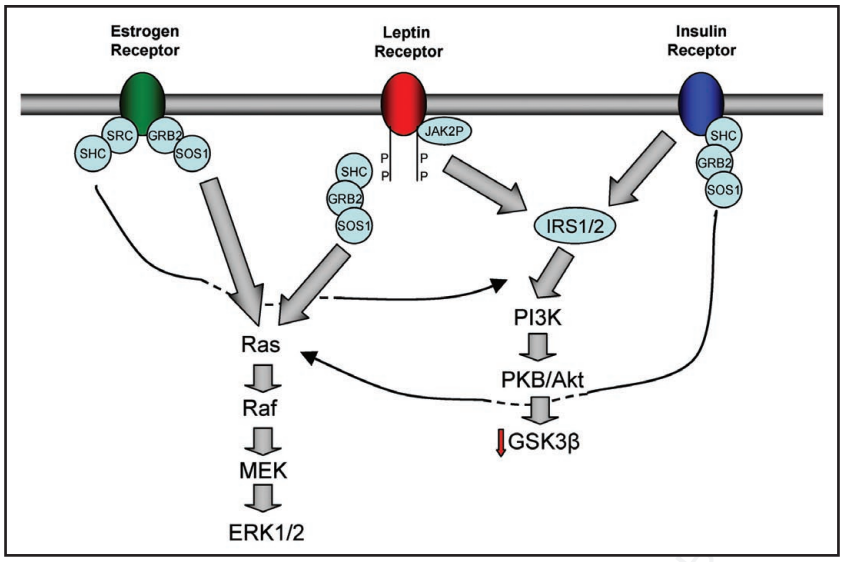

Figure 1. Simplified, schematic diagram showing how leptin, estrogen and insulin signalling may converge upon the same signalling pathways in order to modulate hippocampal synaptic plasticity and dendritic morphology. Upon appropriate ligand binding either receptor is capable of activating either the Ras/Raf/MEK or the PI3K/Akt signalling cascades, both of which have been implicated in various forms of hippocampal synaptic plasticity.

performance in hippocampal dependent memory tasks in response to a specific ERβ agonist and not to an ERα agonist.

It is likely that hippocampal function is altered via a combination of genomic and non-genomic effects depending upon the specific subregion or cell type. It is also possible that some effects may require a genomic and non-genomic component and that these two signalling mechanisms act together to mediate a common goal.

Concluding Remarks

Hippocampal function and modulation of hippocampal function is an area of great interest and an area that has been extensively investigated. Evidence is mounting that hormonal regulation of hippocampal cellular events such as synaptic plasticity plays a vital role in the way the hippocampus functions. As the list of hormonal modulators of hippocampal activity and indeed CNS activity increases, it is becoming clear that these hormones play a vital role.

It is clear from the above data that all three hormones discussed can modulate hippocampal function in similar ways. Given their closely associated functions it is likely that these three systems interact in the hippocampus although evidence of this is scant. In other systems a number of studies indicate that leptin and insulin signalling can converge at a number of points. Leptin reduces insulin-induced glucogenesis and tyrosine phosphorylation of IRS-1 by insulin.[125] Also, effects of insulin on hepatic glucose metabolism are enhanced by leptin.[126] A number of effects mediated by both these hormones involves modulation of PI3K signalling, which may act as a point of convergence for the different systems. In hypothalamic neurons for example, the activation of K_{ATP} channels by leptin is mimicked by insulin[127] and this activation is mediated by PI3-kinase in both cases.[128,129]

Two major signalling systems, the PI3K/Akt and the Ras/Raf/MEK pathways can both be activated by either estrogens, insulin or leptin via activation of their respective receptor complexes (Fig. 1). PI3K and GSK3β have both recently been shown to be involved in either AMPA receptor trafficking or synaptic plasticity in the hippocampus[67,130,131] so it is therefore possible that this signalling pathway could form a point of convergence for the modulatory effects ascribed to these three hormones. Furthermore, the Ras/Raf/MEK signalling cascade has also been shown to be involved in a number of forms of synaptic plasticity in the hippocampus[132] and so could provide an additional point of integration for the actions of these three hormonal systems in hippocampal neurons.

What is clear is that a greater understanding of hormonal signalling and the interplay between different hormonal and neuronal systems is vital to understanding the complex mechanisms underlying processes such as synaptic plasticity and the modulation of dendritic morphology.

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